PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4-32326A	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/00802	International filing date *(day/month/year)* 27.01.2003	Priority date *(day/month/year)* 28.01.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/506, A61K31/00		
Applicant HYKS-INSTITUUTTI OY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21.08.2003	04.05.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Loher, F Telephone No. +49 89 2399-7839

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/00802

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-12 as originally filed

Claims, Numbers

1-20 received on 07.04.2004 with letter of 26.03.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 6-14 (IA)

   because:

   ☒ the said international application, or the said claims Nos. 6-14 (IA) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-15,19,20
	No:	Claims	16-18
Inventive step (IS)	Yes:	Claims	1-15
	No:	Claims	16-20
Industrial applicability (IA)	Yes:	Claims	1-5,15-20
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 6-14 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 99 03854 A (NOVARTIS ERFIND VERWALT GMBH ;NOVARTIS AG (CH); BUERGER HANS MICHA) 28 January 1999 (1999-01-28)

If not mentioned otherwise, the relevant passages are those mentioned in the International Search Report.
Assuming a valid priority of the present application the P-documents cited in the International Search Report are not dealt with during the PCT-phase.

Art 33(2) The present application does not meet the requirements of Article 33(2) PCT, since the subject-matter of amended claims 16, 17 and 18 is not new.

D1 discloses the use of a combination of imatinib and corticosteroids or of imatinib and cyclosporine A. Synergism between the combination partners is disclosed as well. The functional definition "synergistically effective amounts" as used in amended claim 16 and 18 of the present application does, therefore, not confer novelty to the claimed subject-matter with regard to the disclosure of D1. Therefore, the subject-matter of amended claims 16, 17 and 18 is not new in the light of D1.

Art 33(3) The present application does not meet the requirements of Article 33(3) PCT, since the subject-matter of claims 15-19 does not seem to involve an inventive step.
D1, which is considered to represent the most relevant state of the art, discloses synergistic effects of the combination of imatinib and corticosteroids.
The problem to be solved by the present invention may be regarded as how to provide an improved treatment of rheumatoid arthritis.
The present application suggests to solve the problem posed by using imatinib for the treatment of rheumatoid arthritis.

Taking into account the teaching of the cited prior art the following reasoning applies:

With respect to the subject-matter of claims 16, 17 and 18 the applicant's attention is drawn to the fact that even if novelty could be established over the above-cited prior art it is at present not clear wherein an inventive step may reside.

With respect to the subject-matter of claims 19 and 20 the applicant's attention is drawn to the fact that there seems to be no basis for inventive step within the present application as filed since no evidence can be found that the features which are novel result in a solution of the posed problem which could not have been foreseen by the skilled person. As D1 clearly teaches a synergism between imatinib and glucocorticosteroids or cyclosporine A it is a straight-forward option to choose prednisone or cyclosporine A out of one list comprising compounds that act synergistically with imatinib to provide such a composition. The molar ratios are inherently achieved using standard doses of both compounds.
Since there is no surprising effect resulting from the choice to combine either prednisone or cyclosporine A with imatinib the solution proposed in present claims 16-20 is not considered to be inventive in the sense of Article 33(3) PCT.

The subject-matter of claims 1-15 seems to involve an inventive step in the

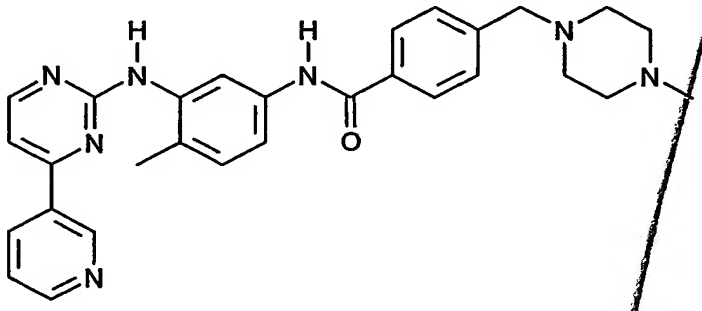
sense of Article 33(3) PCT. At the priority date of the present application there was no hint in the art that would have directed the skilled man to use imatinib, either alone or in combination with a DMARD, in the treatment of rheumatoid arthritis.

Art 33(4) For the assessment of present claims 6-14 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The subject-matter of claims 1-5 and 15-20 is considered to be industrially applicable in the sense of Art 33(4) PCT.

Claims:

1. The use of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-yl-amino)phenyl]-benzamide of the formula I



(I)

or a pharmaceutically acceptable salt thereof for the manufacture of pharmaceutical compositions for the treatment of rheumatoid arthritis.

2. The use according to claim 1 wherein 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide of the formula I is in the form of a pharmaceutically acceptable acid addition salt.

3. The use according to claim 2 wherein 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide of the formula I is in the form of the monomethanesulfonate salt.

4. The use according to anyone of the preceding claims for the treatment of severe rheumatoid arthritis.

5. The use according to anyone of the preceding claims for the treatment of DMARD-resistant rheumatoid arthritis.

6. A method of treating humans suffering from rheumatoid arthritis which comprises administering to said human in need of such a treatment a dose of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide of the formula I or a pharmaceutically acceptable salt thereof.

7. The method according to claim 6 wherein the compound of formula I is in the form of the monomethanesulfonate salt.

8. The method according to claim 7 wherein the monomethanesulfonate salt the compound of formula I is administered at a daily dose corresponding to 100 to 1000 mg of the compound of formula I free base.

9. The method according to claim 8 wherein the daily dose corresponds to 200 to 800 mg of the compound of formula I free base.

10. The method for according to anyone of claims 6 to 9 wherein the administration is once daily for a period exceeding 3 months.

11. A method of treating mammals suffering from rheumatoid arthritis which comprises administering to said mammal in need of such a treatment a pharmaceutical composition comprising
(a) a dose, effective against rheumatoid arthritis, of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide of the formula I or a pharmaceutically acceptable salt thereof and
(b) a therapeutically effective amount of a second drug selected from the disease modifying arthritis rheumatoid drugs (DMARDs).

12. The method according to claim 11 wherein the second drug (b) is a non-steroidal anti-inflammatory drug.

13. The method according to claim 11 wherein the second drug (b) is an anti-inflammatory steroidal drug.

14. The method according to claim 13 wherein the second drug (b) is prednisone.

15. A combination which comprises (a) 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide of the formula I or a pharmaceutically acceptable salt thereof and
(b) a second drug selected from the disease modifying arthritis rheumatoid drugs (DMARDs).

16. A combination according to claim 15 wherein the combination partners are present in synergistically effective amounts.

17. The combination according to claim 15 or 16 wherein (b) is prednisone.

18. A combination according anyone of claims 15 to 17 wherein the molar ratio (a)/(b) of the combination partners is between 0.1 to 10.

19. A combination according to claim 18 wherein the molar ratio is between 0.3 to 3.